PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference SCB 784 PCT	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/EP 03/05551	International filing date *(day/month/year)* 27.05.2003	Priority date *(day/month/year)* 04.06.2002
International Patent Classification (IPC) or both national classification and IPC A61K38/17		
Applicant PHARMAPRODUCTS UK LIMITED et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 6 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
10.12.2003	18.08.2004
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Hars, J Telephone No. +49 89 2399-7825

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP 03/05551

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-6 as originally filed

Claims, Numbers

1-2 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).

   ☐ the language of publication of the international application (under Rule 48.3(b)).

   ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   ☐ contained in the international application in written form.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority in written form.

   ☐ furnished subsequently to this Authority in computer readable form.

   ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   ☐ the description, pages:

   ☐ the claims, Nos.:

   ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1
	No:	Claims	2
Inventive step (IS)	Yes:	Claims	1
	No:	Claims	2
Industrial applicability (IA)	Yes:	Claims	1,2
	No:	Claims	

2. Citations and explanations

see separate sheet

Reference is made to the following documents:

D1: WO 98 42366 A (MERONI PIER LUIGI ;ZETESIS SPA (IT); PANERAL ALBERTO (IT); BARTORE) 1 October 1998 (1998-10-01)

D2: PANERAL A E ET AL: 'CHRONIC ADMINISTRATION OF UK-114, A MULTIFUNCTIONAL EMERGING PROTEIN, MODULATES THE TH1/TH2 CYTOKINE PATTERN AND EXPERIMENTAL AUTOIMMUNE DISEASES' ANNALS OF THE NEW YORK ACADEMY OF SCIENCES, NEW YORK ACADEMY OF SCIENCES, NEW YORK, NY, US, vol. 876, 1999, pages 229-235, XP000971426 ISSN: 0077-8923

D3: NICOLETTI FERDINANDO ET AL: 'Prevention and treatment of lethal murine endotoxemia by the novel immunomodulatory agent MFP-14.' ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, vol. 45, no. 5, May 2001 (2001-05), pages 1591-1594, XP002253826 ISSN: 0066-4804

D4: WO 99 43340 A (ZETESIS SPA ;SANTI CESARE (IT); BARTORELLI ALBERTO (IT)) 2 September 1999 (1999-09-02)

D5: WO 00 78329 A (ZETESIS SPA ;PANERAI ALBERTO (IT); BARTORELLI ALBERTO (IT); NICOLE) 28 December 2000 (2000-12-28)

D6: DATABASE BIOSIS [Online] BIOSCIENCES INFORMATION SERVICE, PHILADELPHIA, PA, US; July 2001 (2001-07) KHASKHELY NOOR MOHAMMAD ET AL: 'Pre-exposure with low-dose UVA suppresses lesion development and enhances Th1 response in BALB/c mice infected with Leishmania (Leishmania) amazonensis.' Database accession no. PREV200100345475 XP002253827 & JOURNAL OF DERMATOLOGICAL SCIENCE, vol. 26, no. 3, July 2001 (2001-07), pages 217-232, ISSN: 0923-1811

Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

V.1 INVENTION

Treatment of leishmaniasis in humans and animals with protein UK114 alone or in combination with ubiquitin (UK110). Claimed is the first and second medical use.

V.2 CLARITY

Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in the documents D2,D6 is not mentioned in the description, nor are these documents identified therein.

V.3 PRIOR ART

If not otherwise specified, subject matter of cited documents relates to the passages indicated in the search report.

D1 - WO9842366
UK114 alone or in the liver extract UK101, containing UK114 and two other proteins of 50 and 10 kDa for the treatment of diseases involving TNF hyperproduction. UK114 lowers TNF-production.

D2 - XP000971426
Use of UK114 as immunomodulator inducing a shift toward a Th2 cytokine profile (increasing IL-4 and downregulating IFN-gamma, IL-2 and TNF-alpha). UK114 was used to treat adjuvant-induced arthritis and diabetes, both characterised through a Th1 cytokine profile. Shifting the Th1 to Th2 pattern delayed the development of symptoms and reduced severity.
The aspect of reducing TNF-alpha production is interesting in the light of other autoimmune and inflammatory diseases.

D3 - PREV200100240573
MFP-14 (=UK114) is used to prevent and treat murine endotoxemia, for its Th1/Th2 shifting properties, related to the reduction of production of TNF-alpha and IFN-gamma.

D4 - WO9943340
UK101 or ubiquitin and UK114 for the treatment of cancer.

D5 - WO0078329
UK114 is used to prevent organ rejection.

D6 - PREV200100345475
Pre-exposure with low-dose UVA suppresses lesion development and induces a response switch from Th2 to Th1 pattern (upregulation of IFN-gamma, TNF-alpha; downregulation of IL-4 and IL-10) in BALB/c mice infected with Leishmania (Leishmania) amazonensis.

V.4 NOVELTY

Remarks under Art. 33(2) PCT

Claim 2 is anticipated by documents D1-D5.

NOTE:
Claim 2 is currently formulated as a first medical use claim ('A pharmaceutical composition'). A first medical use claim is characterised solely by the pharmaceutical composition itself. Any treatable diseases mentioned in such a claims are optional technical features that are ignored when assesing novelty and inventive step.

Claim 2 therefore appears to be not novel according to Art. 33(2) PCT.

V.5 INVENTIVE STEP

Remarks under Art. 33(3) PCT

Document D6, which is considered to represent the most relevant state of the art, discloses a low-dose UVA treatment of leishmaniasis aiming at shifting the immune response from a Th2 to a Th1 pattern, from which the subject-matter of claim 1 differs in that UK114 is used to treat leishmaniasis.

The technical effect achieved is the succesful treatment of leishmaniasis.

The problem to be solved by the present invention may therefore be regarded as how to provide an alternative therapeutical approach for the the treatment of leishmaniasis.

The solution proposed in claim 1 of the present application can be considered as involving an inventive step (Article 33(3) PCT) for the following reasons.

The effect of UK114 on the immune response in mammal was described in D2 to induce a shift from a Th1 to a Th2 pattern, contrarily to what was believed to be necessary in D6. D2 encourages to seek other autoimmune diseases characterised by a TNF-hyperproduction. However, D6 actually aims at increasing TNF-alpha production. The combined knowledge of D6 and D2 would thus have led the skilled person away from the subject matter of claim 1.

Claim 1 appears to be inventive according to Art. 33(3) PCT.